

EXHIBIT A7

Talc in Liver Tissue of Intravenous Drug Abusers with Chronic Hepatitis

A Comparative Study

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To determine the frequency of talc microcrystals in liver tissue of intravenous (IV) drug abusers and the significance of this finding, the authors reviewed, with light and polarizing microscopy, sections of liver tissue from 70 patients with chronic hepatitis and a history of active (45) or past (25) IV drug abuse. Birefringent crystalline particles consistent with talc were found in 44 cases (63%), 31 associated with active and 13 with past drug abuse. The microcrystals were situated predominantly in hypertrophied portal macrophages; there were no well-formed granulomas. Scanning electron microscopic and energy-dispersive spectrophotometry performed on eight of the positive cases showed the characteristic "flake-pastry" appearance and chemical composition (silicon and magnesium) of talc. For comparison, the authors similarly examined 70 cases of posttransfusion chronic hepatitis, all of which had negative findings for talc, and 70 cases of chronic hepatitis with no documented risk factors for viral hepatitis, of which two had positive findings for talc, even though IV drug abuse was denied by the two patients. The authors conclude that talc is frequently present in the liver of IV drug abusers and whenever encountered it strongly suggests IV drug abuse. Only two patients (1.4%) with a negative history also had talc. (Key words: Talc; Microcrystals; Intravenous drug abuse; Chronic hepatitis; Viral hepatitis) *Am J Clin Pathol* 1989;92:583-588

TALC (hydrous magnesium silicate) is an insoluble crystalline material used as a "filler" in certain pharmaceutical drugs meant for oral use. After illicit intravenous injection of some of these drugs, talc microcrystals can be found in various organs and tissues, including the lungs, liver, spleen, heart, lymph nodes, bone marrow, thyroid, adrenals, brain, kidneys, skin, and eyes.^{2,3,6-10,14-17,19,20,24,26,27,30,32,34,37,40,41} Several reports have emphasized the deleterious effects of talc on the pulmonary parenchyma and vasculature,^{2,3,6,7,9,10,14,20,24,34,40} but, to our knowledge,

there are very few studies^{8,15,26,37} focusing on the findings in the liver. Because liver biopsies are not infrequently performed on these patients because of abnormal liver tests,^{4,8,15,22,26,35} we undertook a study to determine the frequency of talc microcrystals in liver tissue of intravenous (IV) drug abusers and the significance of this finding. Other pathologic alterations were also noted, and the findings were compared with those of 70 cases of posttransfusion chronic hepatitis and 70 cases of chronic hepatitis with no known risk factors for viral hepatitis.

Materials and Methods

The clinical histories of 346 cases of chronic active or persistent hepatitis that were submitted for consultation to the Department of Hepatic Pathology of the Armed Forces Institute of Pathology between January 1977 and June 1988 were reviewed. In most cases the reason for histopathologic evaluation of the liver was chronic (> six months) elevation of serum levels of transaminases. A history of current or past IV drug abuse was found in 70 cases. Of these, 11 were submitted from military hospitals, 24 from Veterans Administration hospitals, and 35 from civilian contributors; 67 cases were from 22 different states of the United States and the remaining 3 were from Germany. For each case, the hematoxylin and eosin-stained sections of liver tissue (61 needle biopsies, 5 wedge biopsies, and 4 autopsies) were examined under light and polarizing microscopy to detect the presence of talc microcrystals and/or other foreign material, as well as other pathologic alterations. The amount of talc was graded from 0 to 3+ (0, no talc microcrystals; 1+, 1-10 microcrystals/portal tract; 2+, 11-50 microcrystals/portal tract; 3+, greater than 50 microcrystals/portal tract).

For comparison, we examined, in a similar fashion, the liver biopsies from 70 patients with posttransfusion

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chronic hepatitis and 70 cases of chronic hepatitis with no documented risk factors for viral hepatitis.

Scanning electron microscopic examination and energy-dispersive spectrophotometry were performed on eight cases of chronic hepatitis associated with IV drug abuse and one case of chronic hepatitis with no known risk factors for viral hepatitis. For scanning electron microscopic examination, the paraffin sections were deparaffinized in xylene, cleared in absolute alcohol, mounted on carbon planchets, and carbon coated by vacuum evaporation. They were examined under a Hitachi S-570® scanning electron microscope and analyzed by a Kevex 8000® energy-dispersive spectrophotometer.

Results

Group 1: Cases of Chronic Hepatitis Associated with IV Drug Abuse

The main clinical and histopathologic features are summarized in Table 1. There was a history of active IV drug abuse in 45 cases, whereas the remaining 25 patients had stopped abusing drugs from 8 months to 20 years (mean, seven years) before the liver biopsy or autopsy. The nature of the drugs injected was known in 19 cases (Table 2). Birefringent talc microcrystals were found in 44 cases (63%), 31 associated with active IV drug abuse and 13 with past IV drug abuse (Table 1). The positive cases were from 20 different states of the United States. None of the cases from Germany had positive results.

In each of the 44 positive cases, the portal tracts con-

Table 1. Clinical and Histopathologic Features in the Three Groups of Chronic Hepatitis

Feature	Intravenous Drug Abusers		Patients with Transfusions	Patients with No Known Risk Factors
	Active	Past		
Age (years)				
Range	21-64	19-60	4-81	3-81
Mean	31.4	32.3	52.9	45.9
Sex (M/F ratio)	6.2	2.1	1.3	1.3
Serology				
HBsAg +	16	4	3	8
HBsAg -	10	11	34	40
Unknown	19	10	33	22
Histologic diagnosis				
CPH*	13	9	10	20
CAH†	27	14	47	38
CAH with cirrhosis	5	2	13	12
Talc crystals				
0	14	12	70	68
1+	18	6	0	1
2+	9	4	0	0
3+	4	3	0	1

* Chronic persistent hepatitis.

† Chronic active hepatitis.

Table 2. Nature of Drugs Injected and Amount of Talc in 19 Intravenous Drug Abusers

Drug (no. of cases)	Amount of Talc (no. of cases)
Cocaine (2)	0 (1), 1+ (1)
Heroin (10)	0 (5), 1+ (4), 2+ (1)
Cocaine and heroin (3)	0 (1), 2+ (2)
Cocaine and heroin + Amphetamines (1)	3+ (1)
Barbiturates and amphetamines (1)	3+ (1)
Propoxyphene (1)	2+ (1)
Pentazocine (1)	1+ (1)

tained a variable amount (Table 1) of colorless or lightly greenish, birefringent, needle-shaped particles (Figs. 1 and 2). These appeared single or in small clusters, measured 10 μ m or less in length, and were situated in hypertrophied macrophages (Fig. 2) and occasionally in the wall of blood vessels. The morphologic features of these foreign particles were consistent with those of talc microcrystals. There were no epithelioid histiocytes, giant cells, or foreign body granulomas (Fig. 3). No other type of foreign material, including starch granules, was seen. In addition, there were occasional talc microcrystals in Kupffer cells of the hepatic acini. In two cases, with 3+ talc in portal tracts, numerous microcrystals were noted throughout the acini (Fig. 4).

In all 70 cases, the portal tracts showed a chronic inflammatory infiltrate composed predominantly of small lymphocytes with occasional plasma cells (Fig. 3). Piecemeal necrosis consistent with chronic active hepatitis was seen in 41 cases, whereas 22 showed chronic persistent hepatitis. In seven cases features of cirrhosis were present in addition to those of chronic active hepatitis. Small foci of necrosis within the acini also were frequently encountered. In several cases a mild to moderate degree of fatty metamorphosis was present (Figs. 1 and 3). Table 3 summarizes the different histologic diagnoses in relation to the amount of talc.

Scanning electron microscopic examination performed on eight of the positive cases showed similar findings. The portal tracts contained a variable amount of crystalline material with a typical "flake pastry" appearance (Fig. 5). Similar crystals were seen, occasionally, in Kupffer cells (Fig. 6). Chemically, both silicon and magnesium were identified in the crystals, by energy-dispersive spectrophotometry (Fig. 7).

Group 2: Cases of Posttransfusion Chronic Hepatitis

The main findings are summarized in Table 1. All patients had received blood transfusions from several weeks to years before the liver biopsy; 17 of these received transfusions for various surgical procedures; 11 received transfusions for hematologic conditions; the reason for transfusion was not mentioned in the remaining 42 cases. No talc microcrystals were seen in any of these cases.

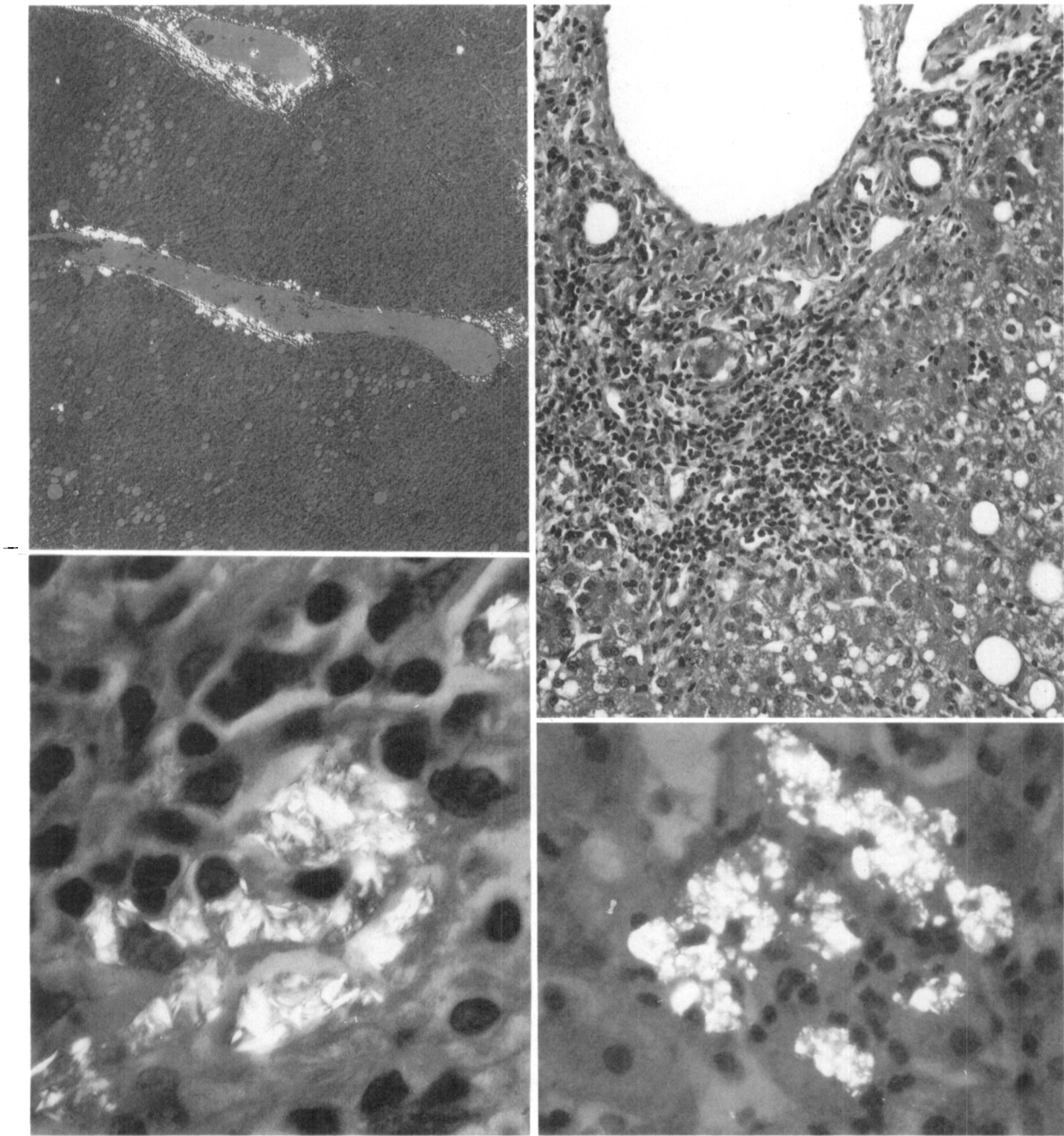


FIG. 1 (upper, left). Wedge biopsy of the liver from an IV drug abuser, showing numerous clusters of talc microcrystals in portal tracts and occasional ones in Kupffer cells of the acini. Hematoxylin and eosin, polarizing light ($\times 40$).

FIG. 2 (lower, left). Clusters of needle-shaped talc particles in hypertrophied portal macrophages. Hematoxylin and eosin, polarizing light ($\times 1,200$).

FIG. 3 (upper, right). Expansion of portal tract by a chronic inflammatory infiltrate associated with mild erosion of the limiting plate. Occasional hypertrophied macrophages are also present, and there is mild fatty metamorphosis. There are no epithelioid histiocytes or granulomas. Hematoxylin and eosin ($\times 200$).

FIG. 4 (lower, right). Aggregates of talc microcrystals in hypertrophied Kupffer cells. Hematoxylin and eosin, polarizing light ($\times 480$).

Group 3: Cases of Chronic Hepatitis with No Known Risk Factors for Viral Hepatitis

The main findings are summarized in Table 1. No known risk factors for viral hepatitis were mentioned in

the clinical history available for these patients. Talc microcrystals were noted in two cases (Table 1), but IV drug abuse was denied by the two patients. Scanning electron microscopic examination and energy-dispersive spectrophotometry performed on one of these cases showed the

Table 3. Histologic Diagnosis Versus Amount of Talc in Intravenous Drug Abusers

Amount of Talc	CAH	CPH	CAH + Cirrhosis
0	14	10	2
1+	18	4	2
2+	6	4	3
3+	3	4	0

characteristic morphologic features and chemical composition of talc.

Discussion

The presence of talc in the lungs of drug abusers and its deleterious effects on the pulmonary parenchyma and blood vessels have been demonstrated previously.^{2,3,6,7,9,10,14,20,24,34,40} Foreign body granulomas, fibrosis, and arteriocapillary occlusion with pulmonary hypertension and cor pulmonale are well-recognized complications. The pulmonary vasculature acts as a filter and blocks the larger talc particles before they can reach the left heart.^{32,41} If the showers of talc particles and the in-

travascular granulomatous reaction are of sufficient intensity to affect the pulmonary circulation, then pulmonary hypertension and a collateral venous blood flow can develop.^{32,41} This would allow a portion of the venous circulation to bypass the lungs and directly enter the left heart and systemic circulation, thus permitting embolization of larger talc particles to various organs, including the liver.

This study addresses several questions: Are the findings in the liver similar to those described in the lungs of IV drug abusers? Does talc cause deleterious effects on the hepatic parenchyma? Which factors significantly affect the amount of talc found in various organs? Is hepatic talcosis a good marker of IV drug abuse?

Our study shows that the findings in the liver are quite different from those described in the lungs of drug abusers. The features observed in the liver included aggregates of hypertrophied macrophages and occasional Kupffer cells containing single or clusters of talc particles and variable degrees of necroinflammatory changes. The terms “granulomatoid”¹⁷ and “pseudogranulomata”²⁶ have been applied to these aggregates of hypertrophied macrophages without well-formed granulomas. They probably represent abortive attempts at granulomatous reaction and



FIG. 5 (left). “Flake-pastry” appearance of talc microcrystals in a portal tract. Scanning electron microscopy (×5,000).

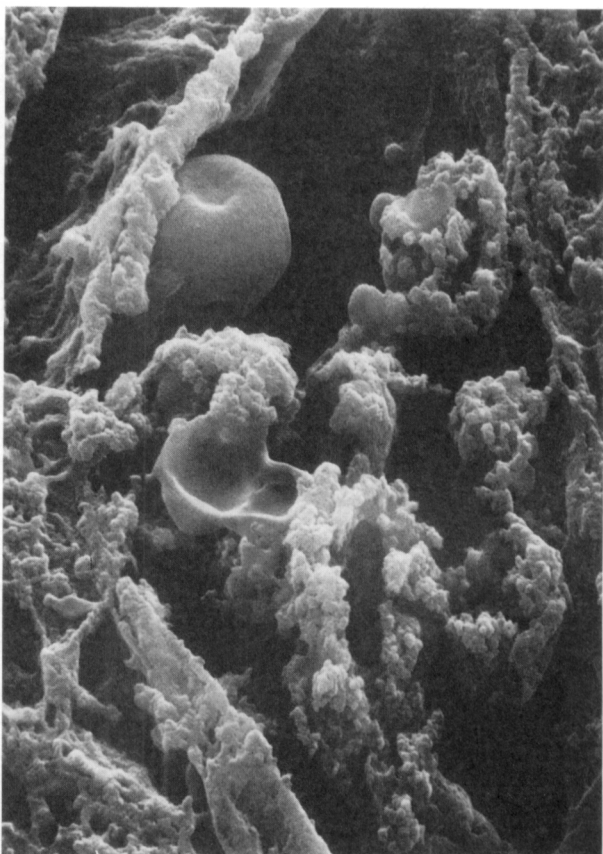


FIG. 6 (right). Aggregates of talc particles in a Kupffer cell lining a sinusoidal space. Scanning electron microscopy (×2,500).

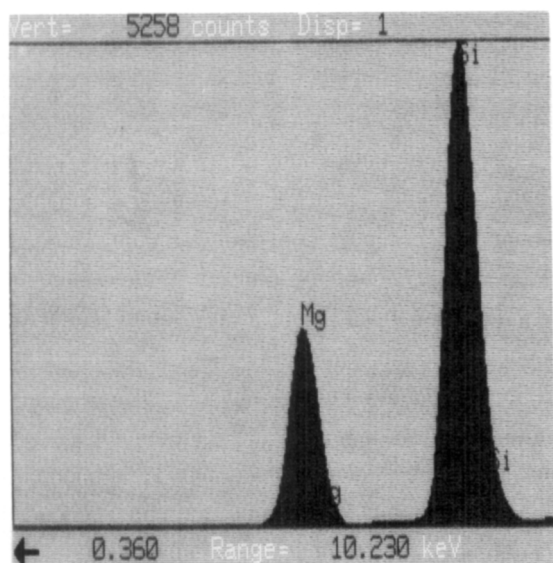


FIG. 7. Energy-dispersive spectrophotometry showing the characteristic peaks for magnesium and silicon, the components of talc.

may be related to the smaller amount and size of talc particles found in the liver in comparison with the lungs.⁶ In contrast to what has been reported in the latter, there were no well-formed foreign body granulomas, no significant fibrosis in most cases, and no other type of foreign material in our series. From the review of previously reported cases, we found only one report²⁴ describing and illustrating convincingly a true granulomatous reaction to talc in portal tracts. In one study,²⁶ starch granules, in addition to talc, were noted in liver biopsies of drug users.

It has been suggested that the filler substances, including talc, found in intravenously injected drugs may play a role in the pathogenesis of liver disease of drug users.^{8,26} Abnormal liver function test results are frequent among drug abusers,^{4,8,15,22,26,35} and a high incidence of HBsAg seropositivity also has been reported in older studies^{4,26,35} and in our own. The various necroinflammatory changes observed in the liver parenchyma, *e.g.*, mononuclear cell infiltrates with or without piecemeal necrosis, were quite similar to those noted in the biopsies of patients with chronic hepatitis not related to IV drug abuse. In contrast to the findings in the lungs, which included fibrosis,^{3,6,9,24} the presence of cirrhosis in the liver biopsies or autopsies, which could correspond to severe fibrosis in the lungs, was noted in only 7 (10%) of our 70 IV drug abusers: 5 of 44 (11.4%) who had talc and 2 of 26 (7.7%) who did not. Higher percentages of cirrhosis were found in patients of the posttransfusion group (18.6%) and in those with chronic hepatitis with no known risk factors for viral hepatitis (17.1%). In addition, the severity of liver damage was not related to higher amounts of talc (Table 3); the ratio of chronic active to chronic persistent hepatitis was higher for the patients with 1+ talc as compared with those with 2+ or 3+ talc, and there were no cases of cirrhosis in the group with 3+ talc. Therefore, we believe

that the necroinflammatory changes and abnormal liver function test results observed in IV drug abusers are probably related to viral hepatitis (B, delta or non-A non-B). If talc particles play a role, it is probably of minor importance.

Several factors may account for the variable amount of talc found in the lungs, liver, and other organs. The association between pulmonary and systemic talcosis and the intravenous injection of pharmaceutical drugs meant for oral use is well known.^{2,3,6-10,14,15,20,27,32,40,41} Propoxyphene, methadone, paregoric, morphine, methylphenidate, tripeleminamine, pentazocine, secobarbital, and phenmetrazine are among the most frequently injected talc-containing drugs. Some authors^{3,34,40} have pointed out the absence or sparsity of talc in the viscera of "pure heroin" users. These findings are similar to our own: talc crystals (from 1+ to 3+) were found in all four patients injecting drugs meant for oral use (alone or with narcotics); in contrast, talc (1+ or 2+) was found in only 8 of the 15 patients using heroin and/or cocaine. The amount and duration of self-injection of talc-containing drugs is not easy to evaluate because reliable and precise clinical histories are difficult to obtain from these patients. Some authors²⁷ believed that the presence of talc in organs other than the lung was dose related. In a previous study on talc emboli to the retina,³² no talc particles were found in patients injecting methylphenidate for less than a year, suggesting that a certain period of time was necessary before systemic talcosis can be observed. This is probably related to the gradual and relatively slow development of a collateral venous blood flow secondary to increasing pressure in the vascular system of the lungs.

Although a lower incidence of positive cases was found among the past drug abusers (52%) in comparison with the active ones (68.9%), talc microcrystals were noted as long as 20 years after IV drug injections had been stopped. Therefore, a history of active *versus* past IV drug abuse probably is not highly significant in regard to the presence or absence of talc in various organs.

It has been reported that the incidence and degree of involvement of the lungs by talc varies with different geographic locations.^{10,34} This is probably related to the availability of "pure heroin" or other illicit drugs as compared with pharmaceutical drugs. In our study, talc was a fairly uniform finding throughout the United States because the positive cases were from 20 different states of 22 from which they were received. The absence of talc in the three cases received from Germany suggests the use of pure illicit drugs.

Finally, sampling problems, *e.g.*, small biopsy containing very few portal tracts, cannot be excluded as a possible factor accounting for some of our negative cases.

From the results of our study, we conclude that talc is a good and useful marker of active or past IV drug abuse because positive findings were noted in 63% of IV drug users, although the presence of talc in two patients (1.4%)

with no history of drug abuse cannot be readily explained. Other sources of talc have been reported. It has been a component of absorbable dust powder used on surgical gloves,^{12,13,31,39} but it appears highly improbable that this could have been the source of talc found in the liver parenchyma, for the following reasons: (1) talc has been largely replaced by starch, as a component of glove powder^{12,13,31,39}; (2) after surgery, talc is usually found on the surface of various organs (and not in the parenchyma) and is associated with a well-formed granulomatous reaction^{12,13}; and (3) it was not found in any of our patients of the posttransfusion group who had surgery. Talc granulomas also have been noted in the skin, after topical application of talc-containing powder or deodorant,^{36,38,43} and, although it has been suggested³⁶ that systemic dissemination may occur from this source, to our knowledge, this has not been clearly demonstrated. The latter assessment also applies to talc-induced pneumoconiosis,^{18,23,25,33,42} pulmonary talcosis after the use of cosmetic talcum powder,²⁸ ovarian talcosis associated with sanitary napkins,^{5,11,21} and intestinal wall/hernia sac talcosis related to ingestion of talc-containing food or tablets.^{1,29}

Therefore, we conclude that the finding of talc microcrystals in the liver parenchyma strongly suggests IV drug abuse and provides the clinician with significant information that may be helpful in further follow-up and management of the patient.

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